REMARKS / ARGUMENTS

The pending claims are claims 15-18, 25-27, 29, and 44-49. Claims 1-14, 28 and 30-43 are canceled. Claim 15 is amended to provide that the method involves prevention or treating physiopathological changes due to hypergastrinemia, and further provides that the composition comprises a G17 peptide fragment of SEQ ID NO: 1 and either a histamine receptor blocker or proton pump inhibitor. These amendments are supported in the specification, particularly at page 7, lines 2-4; page 16, Example 2, and lines 30-31; and page 18, lines 1-14. Claim 17 is amended in accordance with the election. Claims 25-28 are amendment to make them dependent upon Claim 15. Claim 29 is amended to itemize the physiopathological changes. New Claims 44-49 are supported elsewhere in the specification and provide for additional composition components, including anti-gastrin antibodies. Any subject matter canceled from the claims by amendment is reserved for refiling in a continuation or divisional application filed during the pendency of this application. Applicants further affirm the correctness of the inventive entity in view of the cancellation of the non-elected claims.

No new matter was added by these amendments, which are supported in the original specification.

I. The Invention

Hypergastrinemia is a condition in which unusually high levels of the hormone gastrin (for humans generally in excess of 60 pg/ml) circulate in the blood of an indicated mammal. Prior to the filing date of this application, the publications discussing Hypergastrinemia referred to it as a condition that is associated with, but did not necessarily cause, other pathologies, e.g., pernicious anemia, gastritis, etc. The disorders which were characterized by a variety of symptoms including Hypergastrinemia and which required treatment included colon cancer, ulcers and gastritis. For example, Hypergastrinemia was reported as not necessarily accompanying other gastric disorders, such as gastric cancer. Note that in the specification on page 3, line 2-5, the inventors state that a correlation to serum gastrin levels cannot be found in the majority of patients with gastric cancer.

At the time of the filing of this application, Hypergastrinemia itself was not recognized as a condition that in and of itself was dangerous and required treatment. The present inventors were the first to determine that treatment or prevention of hypergastrinemia prior to the development of symptomatic disease is desirable because even in the absence of other symptoms of gastric disorder, Hypergastrinemia itself leads to disease.

II. Rejection Under 35 USC §102(b)

Claims 15-18 and 29 are rejected as anticipated by Watson *et al* **1996** *Cancer Res., 56*:880-885 (Watson II) or Watson et al 1995 *Int. J. Cancer, 61*:233-240 (Watson I), or U. S. Patent No. 5,607,676 (Gevas I).

The Watson I and II documents are held to teach an immunogen composed of 9 N-terminal residues of gastrin linked to immunogenic carrier, used in raising anti-G17 antibodies that reduced gastrin levels in vivo. Gevas I is held to teach G17 fragments linked to immunogenic carriers which inhibit hypergastrinemia related disorders.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

Watson II refers to a study of the effect on the *in vivo* growth of rat colon tumor cells DHDK12 of immunization of the rats with the conjugate formed by glycine-extended gastrin 17 peptide linked to a diphtheria toxoid (DT) (Gastrimmune). In conducting this study, Watson II measured the levels of glycine-extended gastrin by radioimmunoassay (RIA), as produced by the cell line *in vitro*. Subsequently, serum gastrin levels of the rats implanted with gastrin-producing tumor cells and immunized with DT was measured with antiserum directed against the C-terminus of G17 and found to be 114.0 pg/ml compared to 68.5 pg/ml in the Gastrimmune-immunized group. One of skill in the art would readily understand that the gastrin levels in animals with gastric cancer noted in Watson II are higher than the gastrin levels produced in patients afflicted with Hypergastrinemia alone. The inventors concluded that the *tumor-induced levels of gastrin* were reduced about 40%. See page 882, column 2.

Watson I is also a report of the effect of Gastrimmune on gastrin-sensitive colorectal tumors, not on Hypergastrinemia unassociated with other gastric symptoms. Watson I also discusses assessment of serum gastrin G17 levels using anti-G17 antibodies in a RIA. The

authors observed on page 237, col. 2, that serum G17 levels were reduced by administration of the anti-G17 anti-sera and that the cell lines demonstrated reduced growth.

The reports of Watson I and Watson II are directed toward the reduction of tumors and do not recognize or treat hypergastrinemia unassociated with cancer. Watson I and II do not demonstrate that the rats had asymtomatic hypergastrinemia. The studies determined that immunization with Gastrimmune raised antibodies that inhibited the growth of the colon tumor cells and reduced tumor-induced levels of gastrin. Neither Watson I nor II provide any suggestion that Gastrimmune decreased gastrin levels in circulation sufficiently to treat hypergastrinemia alone, merely that Gastrimmune reduced the tumor size in the rats had implanted tumor cells. The studies determined that immunization with Gastrimmune raised antibodies that inhibited the growth of the colon tumor cells and reduced *tumor-induced* levels of gastrin.

Because neither Watson I nor II recognized the necessity for treating hypergastrinemia as a disease itself, apart from its presence as a circumstance of cancer, these references do not teach one of skill in the art that treatment of Hypergastrinemia alone is desirable or that it may be effectively treated with Gastrimmune before the onset of physiopathological changes, e.g., tumors, with Gastrimmune.

For purposes of this discussion, Gevas I refers to both US Patent Nos. 5,607,676 and 5,609,870, which have the same specification. The other patents by this inventor include US Patent Nos. 5,023,077 and 5, 622,702, which have the same specification and are referred to herein as Gevas II; and US 5,468,494 referred to herein as Gevas III. As with the Watson references, cited above, and as admitted by the examiner in making the rejection, Gevas I, II and III refer to the treatment or prevention of known diseases, e.g., gastric disease, duodenal ulcer disease and cancers. There is no recognition in these references of the need for the treatment of hypergastrinemia alone, prior to the onset of disease. There is no recognition that hypergastrinemia is itself a disease worthy of treatment. Therefore, nothing in these references addresses any need for treatment, or method of administration, or dosage, or pharmaceutical composition that would successfully treat hypergastrinemia prior to physiopathological damage resulting in disease. Thus, Gevas I, II or III with their suggested

usages for the treatment or prevention of gastric ulcers or cancers do not teach a method for the treatment of hypergastrinemia alone.

Note that even recent publications demonstrate a lack of recognition that hypergastrinemia is a disease worth treating, and in fact considered it to be a tolerated side effect of treatments of ulcers with proton pump inhibitors (R. Lamberts *et al*, 2001 Digestion, 64:205-213, copy enclosed). Thus, the fact that hypergastrinemia, or high levels of serum gastrin, is a health issue requiring treatment is clearly not yet fully recognized.

In view of these remarks, neither Watson I nor Watson II nor any of the Gevas patents can be interpreted as teaching a method for treating hypergastrinemia. This rejection may be properly withdrawn as against claims 15-18 and 29. Applicants also assert that new added claims 44-49 are novel over Watson I or Watson II or Gevas for the same reasons.

II. Rejections under 35 USC §103(a)

Claims 24-28 are rejected as obvious over Watson I or Watson II or Gevas, further in view of Sundler, 1991 *Acta Oncologica, 30*(4):419-427 (Sundler). The examiner considers that modification to combine pharmaceutical agents all known to be useful in anti-gastrin therapy, would have been obvious to one of ordinary skill to combine use of G17 peptides with omeprazole or ranitidine.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

Claim 24 is canceled, thereby rendering this rejection moot as applied to that claim.

The Watson and Gevas documents are discussed above. The combination of Watson I or II or Gevas with Sundler does not suggest the claimed invention. Sundler discusses the onset of hypergastrinemia, gastrin cell hyperplasia and ECL cell hyperplasia after sustained inhibition of acid secretion resulting from long-term use of a histamine H2 receptor blocker or proton pump inhibitor. Sundler further describes the development of carcinoids in the stomach through the proliferation of ECL cells, even after inhibition of acid production. This is similar to the Lamberts reference, cited above. Sundler does not suggest that anything should be/can be done about this situation; it merely asserts that there is a link between ECL cancer and drug-induced hypergastrinemia. Thus, Sundler coupled with the primary

references does not provide the suggestion that there is a need for the treatment of hypergastrinemia alone, prior to the onset of disease. The combination of this observation of Sundler with Gevas or Watson does not acknowledge that hypergastrinemia is itself a disease worthy of treatment. Therefore, nothing in these references addresses any need for treatment, or method of administration, or dosage, or pharmaceutical composition that would successfully treat hypergastrinemia prior to physiopathological damage resulting in disease.

Further, by acknowledging that the receptor blockers and PPIs initiate a cascade of event including hypergastrinemia and cancer, Sundler effectively appears to ***teach away*** from the use of such reagents to treat hypergastrinemia.

Thus, no combination of these references suggests the combined therapy of the present invention for preventing the development of hypergastrinemia even prior to development of other symptoms. No combination of these references suggests that adding reagents that cause hypergastrinemia to a method for reducing gastrin would likely have any effect in treating hypergastrinemia. The cited references do not suggest the present invention.

In view of the amendments and these remarks, Applicants respectfully request reconsideration of this rejection.

Applicants respectfully request that these claims be found allowable and be passed to issuance in due course.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper, or credit any overpayment in any fees, to our Deposit Account Number 08-3040.

Respectfully submitted,

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